General Comments:

- For the HRRA, there is an inherent tension and competition between the need to produce various assessments in a timely fashion and to incorporate strategies based in “new and emerging” science into its activities. This inherent tension needs to be explicitly acknowledged and considered as priorities are set.
- The present plan provides a straightforward description of activities within the four themes, but neither provides a strong overall vision nor identifies points for synergism across the four components. These limitations of the current plan are well recognized and will be addressed by Dr. Olden and his team.
- With an extensive portfolio of risk assessment activities, the HRRA provides a superb platform for carrying out applied research. An agenda of research should be maintained that builds from this opportunity.

- The present document focuses on technical elements of the four themes, but gives insufficient attention to sustainability, which is inherently within the scope of HRRA.
- The HRRA should assure that its network of collaborations in risk assessment reaches as broadly as possible within EPA and also extends to incorporate partners outside the agency, whether in government, academia, or other sectors.
- A plan is needed for training in risk assessment that reaches to new scientists and practitioners in the agency, that keeps the staff at the “cutting edge”, and that educates decision-makers, keeping them abreast of the newest approaches.
- EPA should carefully examine the placement of the risk sciences within the Agency to assure that there is sufficient integration and connection among risk scientists. Are the risk scientists sufficiently connected?

1. FIRST YEAR PROGRESS

Charge Question: How are the ORD research programs progressing in the first year of implementation? Are the research activities planned for FY 13 and future years appropriate for answering the science questions in the Strategic Research Action Plan?

- Recognizing that the timeframe for assessing progress is quite limited, progress was judged to be fully satisfactory.

- Priorities still need to be assigned to some items within several themes, particularly 3 and 4. The methodology of risk assessment is an element of Themes 3 and 4 and it is also prominent in the themes of *Chemical Safety for Sustainability* (CSS). Thus, the methods of risk assessment are mingled with the problems to which they are being applied. This mingling seems to have been problematic previously as the positioning of HHRA was considered; the current integrative diagram (Figure 4 in *EPA Research Program Overview 2012-2016* reflects this difficulty.

- Within CSS and HHRA, risk assessment methods are mentioned extensively. While cross-program integration is proposed, the relevant agendas within these two programs are largely separated and the basis for selecting outputs and giving them priority is not clear. Even within HHRA, there is not adequate connection and synergy. For example, transparent evidence synthesis is integral to both the IRIS Program and the development of the ISAs, but this connection is not made.

- Additionally, HHRA, as for other programs, would benefit from the integration of social, behavioral, and decision scientists into the activities related to risk assessment methodology in support of decision-making. This recommendation from the prior review remains relevant.

2. SUSTAINABILITY

- **Charge Question: How are ORD programs contributing to sustainability through their research plans and activities? What advice does the SAB and BOSC have for each research program about advancing sustainability in future research?**

- In our view the key to sustainability is the integration of the science, communication across all program areas and implementation of the science to address community concerns and problems.
- Not explicitly stated in HHRA plan on how to make the links-timely prediction of risk to reduce harm
- The key to accomplish this is the continued training of EPA scientists and staff in methods to undertake the steps to meet the goals of the plan. It seems to me that more details are needed to outline the specific aims to ensure sustainability.

3. BALANCING IMMEDIATE PROGRAM NEEDS AND EMERGING ISSUES

- **Charge Question: As we consider science for the future, while budgets continue to shrink, how should ORD balance its commitments in the Strategic Research Action Plan with the need to advance science on emerging issues?**
- EPA might consider the development of cooperative agreements with outside parties via the Federal Technology Transfer Act (FTTA), or linking with the Agency for Toxic Substances and Disease Registry (ATSDR) for jointly developing PPRVTs and Minimal Risk Levels, or linking with ATSDR, the State of Minnesota and/or EPA's Office of Water for developing dose response assessment values of various durations (Dourson).
- EPA should respond an emerging problem through the use of of emerging tools as a way to improve their utility, efficacy, and acceptance (Shubat).
- EPA should consider the use of shorter term testing to improve the basis of the risk assessment (Stram).

- EPA should consider active partnering with other entities for building opportunities to use high throughput testing and new observational studies based on established cohorts (Samet).
- EPA should consider the routine use of screening levels, similar to established Thresholds of Toxicology Concern (TTC) or the developing concept of Conditional Toxicity Value (CTP) (Shubat).
- EPA should incorporate a process to prioritize themes 3 and 4 of the HHRT given the possibility of limited resources (?).
- SAB should propose transformational ideas, such as EPA's HERO, as a way of leaping the program forward (Vandenberg).
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- **Human Health Risk Assessment Charge Questions:**
- **The HHRA research program is committed to modernizing methods to evaluate the health effects of pollutants, consistent with advice of the SAB/BOSC and National Academy of Sciences. What aspects of the hazard and dose-response assessments produced by the HHRA research program are most likely to benefit from the application of state-of-the-art data streams and methods (e.g., in vitro toxicity testing results, gene expression profiling data, bioinformatics and QSAR modeling)? Additionally, what approaches can be envisioned to enhance risk managers' understanding, use and acceptance of these new methods? HHRA can use new knowledge to inform strength of evidence for risk assessment and decision making how to weigh the new evidence and use it in RA Process??**

- Potential benefits to develop RAs in shorter time with more objective information from newer tests
- Insights into mode of action: can inform cross-species translation, effect, dose response curve using framework of mode of action.
- It seems obvious that the IRIS assessments will benefit substantially from new data and new risk assessment methods. The IRIS program is at a point where it is under some pressure to 'reinvent' itself, because of criticisms the program has endured (some fair, and some unfair) over the past year.
- There are great opportunities to 'reinvent' the IRIS program by doing three main things: (1) substantially shortening and streamlining the documents to make them easier to use and to review, (2) incorporating Tox21 data, initially in qualitative discussions, then in parallel with traditional toxicology data, and ultimately as part of critical pathway-based extrapolations, and (3) incorporating the key recent recommendations from the NAS on reforming risk assessment, with a particular focus on grappling with cumulative risk, making implicit defaults explicit, better characterizing uncertainty, and exploring the unified dose-response.
- These points are all reflected in the Strategic Research Action Plan, although perhaps not as clearly as they could be.

- Rapid turn-around risk assessments and crisis-level technical support may need to rely almost exclusively on some of the new data streams and methods in the near future.
- In the short-term, a very productive use of these methods will be to set priorities for developing additional dose-response data and subsequent guidance such as reference doses developed through the IRIS program. There is also an immediate need for comparative risk evaluations for substances that have little toxicity data for use in alternatives assessments for such applications as green chemistry. It appears from the HHRA SRAP that ORD is already working on such applications.

- A high priority should be placed on developing science policy around the question of what is an adverse effect in relationship to interpreting the results of high- and medium throughput testing.

- In the long-term, assurances must be provided that these new scientific methods result in new research that explores and explains the links between environment and health for our most susceptible populations.

- The benefits of state-of-the-art data streams and methods will ultimately be judged by the extent to which the use of these new methods result in faster and more definitive information that is successfully used to protect health through public health programs and environmental health protections.
- It is of major public health importance that IRIS assessments are done in a timely and efficient manner, and multiple rounds of redundant peer reviews are a waste of federal funds without providing any significant added scientific benefit.

- **In the 2010 mid-cycle progress review of the HHRA program the Board of Scientific Counselors noted that "IRIS assessments and ISAs are among the most heavily peer reviewed documents provided by scientists anywhere." How can the HHRA research program efficiently obtain robust peer reviews that contribute to the scientific integrity of assessments without impacting the timely provision of documents with public health value? Additionally, can the SAB/BOSC provide advice on the appropriate overall balance of peer review of individual products versus other recommended scientific capacity-building activities?**

- Excellent overview of peer review process
- Display of reviews and topics good
- Transforming information into quality products based on peer review need to ensure incorporation and response to peer review comments.. have feedback loops and detailed response
- Iterative process needed with timely response
- Judge the value added by response to peer review; peer review coordinator-referee of comments. A tiered, screening strategy might be useful that is reflective of the underlying complexity of the assessment being reviewed. Regardless, “rigorous peer review” cannot be sacrificed to expediency.
- The Agency should have the overall goal of providing its assessments in a timely way. This goal has not always been met, particularly for the IRIS assessment and the past Criteria Documents. More recently, the Agency has been completing the peer review of the ISAs in a timely fashion, in part because of court-ordered deadlines. Additionally, the switch from the Criteria Document to the ISA format has led to more synthetic and transparent documents that can be more readily reviewed. Some of the IRIS assessments that have been tardy in being completed have been overly long and found to be deficient in various ways. The plans to change the process used to carry out the IRIS assessments should enhance peer review.
- ORD appreciates that the intensity of peer review is proportional to the importance of the product. Toxicology reviews, reference doses, and cancer slope factors are extremely important in programs across EPA and in environmental and public health actions carried out across the country. It is likely that the reforms already being implemented in the IRIS program, and that lead to greater transparency and stakeholder involvement early in the review process, will result in less onerous peer reviews. EPA will be able to address more concerns more directly during the review and stakeholders can target their comments more effectively in a peer review.

- The results of peer reviews could become more acceptable and the reviews more efficient if EPA management can more openly discuss the implementation policies or interpretations that could ensue from various aspects of a review (e.g., policy and remediation options that state or EPA risk managers might adopt or might need to adopt based on outcomes), so that the scientific findings can be evaluated with less prejudice concerning the application of the finding.
- Review Process must be robust and efficient
- Chemical assessment advisory committee??

- The release of the three groundbreaking NAS reports (Tox 21, Science & Decisions, and Phthalates) has created enormous scientific pressure on EPA to modernize their overall scientific approach to risk assessment. This modernization needs to occur in parallel with the ongoing production of individual risk assessment products, since there is an ongoing need to provide the best possible current risk numbers for decision makers. The balance of effort should shift toward building EPA capacity to incorporate the new toxicology data into a new risk assessment approach.
- If EPA does not put significant effort into building the scientific capacity to integrate new toxicology data, and to figure out how to implement the recommendations to make defaults more explicit, employ a unified dose-response, and perform cumulative risk assessments, then these important reforms will not happen and EPA will be utilizing outdated science. EPA cannot allow itself to be left behind as the science of toxicology and risk assessment moves forward, so a significant shift of effort is needed.

- **Additionally, what approaches can be envisioned to enhance risk managers' understanding, use and acceptance of these new methods?**
- Training and education tailored to the information needs and backgrounds of the agency risk managers as well as those outside the agency (risk assessors, risk managers, academia, and science advisors to the communities affected by risk management decisions). *(HHRA NP has already given this problem careful consideration by meeting with agency risk managers in a focus group venue to learn how risk managers 'receive' information about risk assessments. The breakout group recommended including training to risk assessors and managers outside of EPA.)*

- Start using new products immediately in qualitative if not quantitative ways in current risk assessments including IRIS reviews. *(HHRA has begun to include and describe –omics data and 'Science and Decisions' innovations in IRIS and other risk assessments and should continue to integrate this information as quickly and effectively as possible as one way to ensure that risk assessors and risk managers become familiar with new types of data and methods and see the utility of the new information)*

- Work closely with programs outside of both ORD and the agency to ensure that other risk assessment programs incorporate new approaches in a consistent manner. *(New approaches and new data will gain greater acceptance by risk assessors and managers if ORD works with other program and other agencies to gain consensus on the use of data and methods)*

- Study the utility of new approaches for decision-making, including presenting side-by-side or integrated assessments of traditional and new approaches. *(Systematically study, perhaps through the use of decision science, the utility of the new data sources for decision-making, and determine how evidence from new areas of investigation should be combined or presented along-side of more traditional methods of risk assessment)Empiric research needed on adoption and innovation of new RA methods!*
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II. DRAFT CHARGE QUESTIONS FOR GENERAL ORD/PLENARY SESSION

1. INTEGRATION ACROSS PROGRAMS

Charge Question: Based on the presentation of five integrated topics, what advice can the SAB and BOSC provide to help ORD succeed in integrating research across the ORD programs? How can different approaches to integration help us achieve our research goals?

- Areas of high integration needs/potential for growth (across all programs)
  - Rapid Risk Assessment
    - e.g. in conjunction with Homeland Security
    - Chemo-toxicity of short-term exposures
    - Input into PAL's (Provisional Action Limits)
  - Integrative models for effects on Children's Health
    - Fill in place between assessment and research
      - Exposure Assessment
      - Computation toxicology
      - Developmental toxicology
    - Bring in
      - Toxicity Models
      - In vivo effects
      - Animal data
      - mechanistic models
      - pathways
- Prioritize integration (since integration has its costs of time and effort -- avoid too many cross agency task forces)

- Outreach may be better word than integration
  - When new issue comes up notify all programs since there may be interest in the same problem from many individuals in other areas
  - Continue past process of listing integrable topics in communications with other programs
  - Formalize plans for integration
    - As on page 13 of document (mention of Research Coordination Team)
    - Find ways that can deal with complex matrix of research partners, stakeholders, etc.
- Regarding the case studies flesh these out further as a learning tool, describe common qualities of which integrations worked, and which ones less so,

2. INNOVATION

Charge Question: How can ORD's initial innovation activities be improved to ensure continued and long term benefits for EPA? Are there useful experiences and lessons from other research organizations about managing innovation? What guidance can the SAB and BOSC provide for ORD in developing innovation….

Challenges that still remain:

- Innovation vs. evolution
- Keeping up the exceptional innovative ideas in the proposal submission over time
- Changing the ORD culture towards more innovation

- Up-Front Metrics: without it research can lose focus rapidly and meander all over the map(black hole)
- Proposal metrics need to be defined and significant enough to be considered innovative (order of magnitude approach)
- Project phase success metrics need to be defined (Skunkworks phase 1/2/3)
- Transition plan needs to be defined up front (What happens after project is done? Customer?/Industry partner?/community partner?)

- Key thrust based on agency mission
- What kind of innovations are critical to support EPA mission

- Role of interdisciplinarity in PIP

  Will proposals require interdisciplinary science or interdisciplinary review of science or both

- Approaches to innovation

  Directed innovation makes more sense than free wheel innovation to satisfy EPA needs
- X-prize engages the public
- Open innovation
- Looking to young investigators for fresh ideas